REMARKS

Specification

By the above amendment, the priority claim now appears at the beginning of the specification.

The expressions "tertiary or quaternary ammonium salt" and "tertiary or quaternary salt" have been amended in order to correctly designate the tertiary amine and the quaternary ammonium salts which are exemplified as pyridine and tetrabutylammonium salts (see the remarks below, concerning claims 17 and 35). The new language is clearly supported by the original disclosure.

Analogously, the word "tetra (C_1-C_4)alkylammonium", exemplified as tetrabutylammonium, is now uniformly indicated in the specification replacing C_1-C_4 trialkylammonium. The word (C_1-C_4)alkyl is commonly used to indicate alkyl groups of from 1 to 4 carbon atoms such that the original disclosure supports the term "tetra(C_1-C_4)alkylammonium"

The phrase inserted at page 21, line 28, after 'and' amends a drafting mistake due to the omission of a piece of sentence between two "and". The missing piece correctly appears at page 21, lines 7-8, page 22, lines10-11, page 23, lines 8-9, page 24, lines 20-21, page 26, lines 4-6, page 27, lines 3-4 and in claims 38, 44, 50, 56, and 59.

Priority

A certified translation in English of IT MI2000A000665 application will be filed in due time.

Claim objection

The correction of the numeral 2,7 appearing in Claim 50 has been made by the above amendment. By changing it to 2.7, the objection is overcome.

Claim Rejections – 35 U.S.C. § 112

By the above amendments made in claims 1, 11, 12, 17, 22, 33-35, 41and 50, said claims now point out and distinctly claim the subject matter which the applicants regard as their invention.

In claim 1, the change of 'N-deacetylate N-sulfate' to "N-deactylated N-sulfated" clearly indicates that said derivatives are N-deacetylated and subsequently N-sulfated.
Also the removal of the expression "on weight" and the sentence "a content in chains with high affinity for ATIII of from 25% to 50% by weight of its chains", as newly formulated, clarify that, in the mixture of chains forming the K5 derivatives (see page 2, lines 7-11 of the specification), from 25% to 50% by weight of said chains have high affinity for ATIII.
The extent of epimerization has been modified to read "epimerised at least to 40%".

In claims 11-12, 17 and 35 the definition of the amine salts has been amended in order to point out that said salts are tertiary amine or quaternary ammonium salts.

In claims 17 and 35, other amendments have been made in order to overcome the 35 U.S.C. § 112 objections. In (iv) and (v), 'treating a salt with an organic base' has been amended to read "treating an organic base salt" in order to avoid any confusion due to the word 'with', which could be considered in combination with 'treating' or with 'salt'. The claim now unequivocally recites that a salt of the O-oversulfated or of the partially O-desulfated product with an organic base is treated with a mixture DMSO/methanol or with an O-sulfating agent, respectively. In particular, at page 11, lines11 and 12, at page 17, lines 9-11 and in Examples 1(e) and 12(iv) the pyridine salt of the O-oversulfated product is prepared, while at page 11, line 26 and in Examples 1(f) and 12(v) the tetrabutylammonium salt is described.

In claim 22, the word 'comprises' has been replaced by the expression "selected from the group consisting of", thus clearly indicating that the reaction is carried out in the presence of C5-

epimerase in one of the disclosed forms.

Claim 33 has been amended in order to correctly recite "into" and to specify that the other salt is that of said glycosaminoglycan, the word 'another' clearly indicating that the salt thus prepared is other than the sodium salt. In this connection, it is submitted that the salt thus obtained may be pharmaceutically acceptable or not. In fact, claim 34 includes a tetra(C_1-C_4)alkylammonium salt which is not necessarily pharmaceutically acceptable but is commonly used in the glycosaminoglycan chemistry and exemplified throughout the specification as tetrabutylammonium salt.

In claim 34, tetra(C_1-C_4)alkylammonium now clearly designates a tetraalkylammonium in which the alkyl group contains from 1 to 4 carbon atoms.

In claim 41, the percent of hydrogen (from about 60% to about 55%) is now referred to the R groups taken together. It appeared to the applicants that the fact of giving the numerals 60% and 55%, for R-R_3 = H, in this order was more elegant, because the highest amount of hydrogen corresponds to the lowest sulfation degree. Thus, when 60% of the symbols R are hydrogen, the sulfation degree is about 2.4 while it is 2.7 when 55% of R-R_3 are H. In any case, this is an only formal question because the substance does not change. Applicants are ready to switch the numerals 60% and 55% if the examiner maintains his position.

Double Patenting

The copending Application No. 09/738879 is abandoned. Thus, the rejection under 35 U.S.C. 101 is overcome.

Joint Inventors

Applicants hereby declare that all of the claims of this application, as filed, are commonly

owned and that, as physical persons, they are the sole and joint inventors of the entire subject matter claimed.

Claim Rejections – 35 USC § 103

Claims 11-13 and 17-62 stand rejected over Lormeau et al. (US 5,550,116), combined with Zoppetti et al. (US 6,162,797) and Branellec et al. (US 5,599,801).

Claims 11-13

The goal of the present application is to provide glycosaminoglycans which are not obtained from animal tissue sources (page 1, lines 22-24 of the specification). The glycosaminoglycans of the invention are quite different from heparin, as shown by their biological parameters and by their structure, in particular because of the presence of a unique content in glucosamine 3-O-sulfate units, from about 17% to about 21% SO_3^-, compared with about 0.5% SO_3^- of heparin (see claim 38 and page 1, line 18). The glycosaminoglycans of the invention are also quite different from the heparosans of Lormeau, et. al., the low molecular weight heparins of Branellec, et. al. and the epimerised K5 derivatives of Zoppettii, et. al., such that the glycosaminoglycans of this invention are unobvious over the combined teachings of these references. The derivatives of claim 1 have not been rejected as obvious in view of the cited references. Since these derivatives are unobvious, methods of preparing these derivatives such as defined in claims 11-13, are also unobvious.

Method Claims 17-34 and Product Claims 35-37

The invention herein, including the novel glycosaminoglycans, results from

(a) the discovery of the action of divalent cations in facilitating the epimerization,

(b) the observation that a six-step process only may allow the obtention of glycosaminoglycans having the best activity coupled with a lowest bleeding potential,

(c) the discovery that under the particular conditions adopted in step (iv) it is possible to obtain LMW glycosaminoglycans retaining the activity of the high molecular weight products they derive from.

The present Applicants have used known methods and techniques, in particular N-deacetylation, N-sulfation, O-sulfation methods and the nitrous depolymerization, as disclosed in the cited references to prepare anticoagulant/antithrombotic agents such as those responding to the characteristics given at page 4, lines 11-12 and 20-34 of the instant application. However, there is no hint or suggestion to combine these methods and techniques, as defined in claims 17-34, to arrive at anti-coagulant/ antithrombotic agents such as those defined in claims 35-37. The Lormeau et al., Zoppetti et al. and Branellec et al. references are mere examples of the state of the art and knowledge of the above references and their combinations could not suggest (a) to use divalent cations for facilitating the epimerization or (b) to combine the six-steps of the process to obtain the desired result, or (c) to carry out step (iv) under particular conditions (which provide particularly interesting LMW products) at the end of the process. Furthermore the combined teachings do not suggest providing the chemical structure, in particular the sulfation pattern of heparin.

Although the individual steps used to prepare glycosaminoglycans were substantially known, how to select and combine these known procedures was an entirely different matter and the results of this combination were anything but expected. In practice, it was impossible to foresee what would be the structure of a "good" product and therefore, the combination of steps to obtain such a product could not be forseen.

Finally, to illustrate the uncertainty in combining known techniques to prepare "good" products, applicants point out that the first goal of the research in this area was to obtain a "biosynthetic heparin" from polysaccharide K5 by reproducing the heparin structure, which was known. Notwithstanding this knowledge and many publications on the biosynthetic heparin, no one has succeeded in obtaining an epimerised K5 glycosaminoglycan having a structure at least close to that of heparin, with the same biochemical profile. This research is still in progress.

Glycoaminoglycans (Claims 38-52), Pharmaceutical Compositions Which Contain Them (Claims 53-62) and Methods Which Use Them (Claims 63-70)

No evidence has been presented to support the rejection of claims 38-72. There is no motivation of direction to prepare compounds having the structures defined in claims 38, 44, 50, 56, and 59, including the sulfation pattern of these compounds. Therefore, these compounds and the compositions which contain them are unobvious. Since the compounds are unobvious, the methods which employ them are unobvious. Therefore, the rejoinder of these claims for allowance is appropriate.

Based on the above remarks, Applicants submit elected claims 1-62 and non-elected claims 63-72 are in a condition suitable for allowance and patentable over the cited references. Therefore, withdrawal of the rejections and allowance of these claims are earnestly solicited.

Respectfully submitted,

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